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Original Article

Retrospective evaluation of platelet indices and RAS mutations in patients with colon cancer

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ABSTRACT

Aims: Colon cancers are one of the most common cancer types in the world and cause significant mortality. The presence of RAS mutation is also associated with poor prognosis in colon cancers and plays an important role in the choice of treatment. Platelet indices, which have recently been evaluated with an easy-to-reach method, have been discussed as an inflammatory marker in many studies. In this study, it was aimed to investigate the relationship between platelet distribution width (PDW), colon cancer stage and the presence of RAS mutation.

Methods: File records of 132 patients who were followed up with the diagnosis of colon cancer in Kırıkkale University Faculty of Medicine, Department of Internal Medicine and Medical Oncology Department between January 1, 2015 and January 1, 2021 were retrospectively analyzed. Patients with RAS mutations and who did not receive chemotherapy were included in the study. Patients with and without RAS mutation were divided into two groups and their platelet index (especially PDW) values were compared. PDW values were compared according to the stages of the patients. The correlation between stage and PDW was examined.

Results: Of the 132 patients included in the study, 82 (62.1%) were male and 50 (37.9%) were female. Participants; 12 (9.1%) stage 1, 23 (17.4%) stage 2, 29 (22%) stage 3, 68 (51.5%) stage 4 colon cancer patients. There were no RAS mutations in 73 (55.3%) patients, and 59 (44.7%) patients had RAS mutations. There was no significant difference in PDW between the two groups with negative and positive RAS mutations (p=0.826). According to the stages; PDW values were significantly different between the four stages (X2=9.878, p=0.020).

Conclusion: In the study, PDW increased as the stage increased, but there was no significant relationship between RAS mutation and PDW. This was attributed to the fact that as the stage increases, the level of inflammation may be associated with an increase. Larger studies on this subject are needed.

Keywords: Platelet indices, colon cancer, RAS mutation

INTRODUCTION

Cancer ranks second among the diseases that cause death, after cardiovascular diseases in Turkey as in many countries.[1] The most common malignancy among gastrointestinal tract cancers is colon cancers. Colorectal cancer (CRC) is the third most frequently diagnosed cancer in men; It is the second most common cause of cancer-related deaths in women after breast cancers, and the third most common cause of cancer-related deaths in the world.[2] According to Surveillance Epidemiology and Results (SEER) in CRC, 5-year survival rate is associated with stage and is 90% in local cancers, 72% in regional cancers and 14% in metastatic cancers.[3]

The Kirsten rat sarcoma (K-RAS) gene is a GTP-dependent membrana protein that acts as a proto-oncogen. It is one of the genetic pathways in the development of CRC.[4] Ras mutations are not only seen in CRC; they are also seen in different incidences in other types of cancer. The most common type of cancer is pancreatic cancers (90%), and this mutation is seen in the rate of lung adenocarcinomas (30%) in CRC (50%), thyroid tumors (50%) and myeloid leukemia (30%).[5] If no RAS mutation is detected in patients with metastatic CRC, it is called wild-type CRC. According to the result of Ras mutation, the chemotherapy protocols given vary. The addition of drugs such as cetuximab and panitumumab (anti-eGFR) epidermal growth factor receptor inhibitors to standard chemotherapy in wild-type CRC has been shown to prolong survival in many previous studies, and it is important for the treatment plan to perform K-RAS and N-RAS mutation analysis before the treatment plan is made.[6]

Many epidemiological studies show that inflammation is also involved in the development of cancer. Cells involved in systemic inflammation are white blood cells and platelets, which also serve as an important risk factor for cancer development. Neutrophils, monocytes, and platelets increase cancer cell proliferation, invasion, and metastasis. FAP and its variants (Gardner syndrome, Turcot syndrome, and

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attenuated familial adenomatous polyposis [AFAP]) occur in less than 1% of all CRCs. Mutation in the adenomatous polyposis coli (APC) gene is responsible for the formation of FAP. Typical FAP usually begins to appear in childhood; it can present symptoms at age 16, and 90% of untreated people develop CRC by age 45. AFAP is diagnosed at a later age than FAP and is diagnosed with cancer later (mean age 44 years for FAP and 58 years for AFAP, respectively).[7] Gardner syndrome includes FAP colonic features as well as extracolonic features (desmoid tumors, epidermoid cysts, lipomas, osteomas (especially in the mandible), fibromas, excess teeth, nasopharyngeal angiofibromas).[8] Turcot syndrome is associated with familial colon cancer and brain tumors (primarily medulloblastomas and gliomas).[9]

Peutz-Jeghers Syndrome is manifested by hamartomatous polyps of the gastrointestinal tract and the classic appearance of mucocutaneous melanin pigmentation. Both the gastrointestinal tract and the extra-intestinal system may increase the risk of malignancy. Juvenile polyposis syndrome is autosomal dominant and has an increased risk of CRC. Patients with juvenile polyposis syndrome have a 39% lifetime risk of developing CRC.[10]

Inflammatory bowel diseases play a role in the development of CRC. The risk of cancer is increased in both ulcerative colitis and Crohn's patients. While the risk of CRC increases 5-15 times in ulcerative pancolitis cases, this risk is 3 times higher in ulcerative colitis cases with left colon involvement. In pancolitis cases, the duration of the disease causes a 2% increase in 10 years and an 18% increase in 30 years, in CRC development. Although there is not enough information on Crohn's patients, Crohn's pancolitis has a risk of CRC similar to ulcerative pancolitis.[11]

Smoking, high-calorie diet, excessive red meat consumption, high saturated fat, excessive alcohol consumption, obesity, and sedentary life have an important place in the risk of developing CRC. Eating foods low in fiber and consuming processed foods also increases the risk of developing CRC. High-fiber foods, aspirin, celecoxib, folic acid, increased physical activity, high-grain diet, consuming fruit and vegetable, eating foods high in calcium, selenium, some vitamins (vitamins D, A, C, E),and fish oil are protective against CRC.Long-term follow-up randomized trials have shown that daily use of 100 mg of aspirin is ineffective in preventing colon polyps, but with a delay of several years, it reduces the risk of CRC.[12]

In our study, it was aimed to compare PDW, an inflammation marker, in CRCs with and without RAS mutation. It was aimed to investigate the change in the increase of PDW with inflammation according to the presence of advanced stage and RAS mutation in CRCs.

METHODS

Study Design

This speciality thesis study was approved by the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 16.06.2021, Decision No: 111). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The medical records of the patients who were followed up with the diagnosis of colon cancer between January 1, 2012 and January 1, 2021 in the Medical Oncology Polyclinic of Kırıkkale University Faculty of Medicine were examined retrospectively. The number of patients to participate in the study was determined as Clincalc.com.tr power alpha: 80%. In the study, 192 patient files were examined. A total of 132 patients were evaluated. The inclusion criteria of the patients were determined as being older than 18 years of age and being diagnosed with colon cancer, documented stage of the disease, knowledge of RAS mutation, and availability of hemogram values. The date of diagnosis was taken as the date of pathological diagnosis. By retrospectively scanning all patient records, age, gender, comorbid disease status, stage, genetic mutation analysis of the patients; K-RAS, N-RAS, neutrophil count at the time of diagnosis, lymphocyte count, platelet index parameters; platelet count, MPV, PDW, PCT, CEA values were determined. The Charlson Comorbidity Score of the patients was calculated to indicate comorbidity. Patients with and without RAS mutation were divided into two groups and hemogram parameters (especially PDW MPW values), stage, survival times were compared and the relationship between them was investigated. Survival was calculated as the time from the moment of diagnosis to death.

Statistical Analysis

Kolmogorov-Smirnov Test was used to determine the normal distribution of the independent variables obtained from the participants. ANOVA-One Way Analysis of Variance Test and Independent Samples T Test were used to analyze parametric variables ($p<0.05$). Tukey Multiple Comparison Test was applied for post hoc analysis ($p<0.05$). Kruskal-Wallis Test and Mann-Whitney U Test were used for non-parametric independent variables ($p<0.05$). Mann-Whitney U Test and Bonferroni Correction Test were used for post hoc analysis ($p<0.0083$). Pearson's Chi-square Test was used to analyze categorical data ($p<0.05$). Pearson's Rho Correlation Test was applied to test the relationship between independent variables. Overall survival was calculated as the difference between the date of diagnosis and the date of death (for any reason) or the date of the most recent information in the medical records. Survival times were estimated by the Kaplan-Meier Survival Test. Survival curves were compared with Log-rank Test, Breslow Test and Tarone-Ware Test ($p<0.05$). Cox-Regression Test was applied to determine the predictivity of independent variables affecting survival times ($p<0.05$). The ROC-Curve Test was used to test the sensitivity and specificity of independent variables that could predict mortality, and the Logistic Regression Test was applied to find the independent variable that could best predict mortality risk ($p<0.05$). The direction and strength of the relationship between study parameters and mortality risk were measured using the Odds Ratio (OR) Test and corresponding 95% confidence intervals (95% CI).

RESULTS

A total of 132 patients, 82 (62.1%) male and 50 (37.9%) female, participated in the study. 12 (9.1%) of the participants were stage 1, 23 (17.4%) of them were stage 2, 29 (22%) of them were stage 3, 68 (51.5%) of them were stage 4 colon cancer patients. 73 (55.3%) of the patients did not have a RAS mutation, and 59 (44.7%) had a RAS mutation.

Participants in the study were divided into two groups as living and exitus. When the data of the two groups were

compared, it was found that there was a difference between the groups in terms of lymph node involvement (Z=7.853, p=0.020), lymphocyte count (Z=-2.568, p=0.010), neutrophil lymphocyte ratio (Z=-2.648, p=0.008), CEA level (Z=-3.684, p <0.001) and CA 19-9 level (Z=-3.111, p=0.002). These findings revealed that lymph node involvement was higher in deceased patients (**Table 1**), lymphocyte count was lower in deceased patients, and CEA and CA 19-9 levels were higher (**Table 2**).

Table 1. Demographic characteristics of living and deceased patients

Variable	Living	Exitus	t / Z	p value
	Average±SS/ The median (min-max)/ N (%)	Average±SS/ The median (min-max)/ N (%)		
Age	62.18±12.01	66.30±14.55	-1.691*	0.093
Sex			0.384‡	0.535
Male	30 (22.7%)	52 (39.4%)		
Female	21 (15.9%)	29 (22.0%)		
Stage			7.690‡	0.053
1	8 (6.1%)	4 (3.0%)		
2	12 (9.1%)	11 (8.3%)		
3	10 (7.6%)	19 (14.4%)		
4	21 (15.9%)	47 (35.6%)		
Tumor			4.777‡	0.189
1	1 (1.4%)	0 (0.0%)		
2	3 (4.2%)	2 (2.8%)		
3	15 (21.1%)	16 (22.5%)		
4	10 (14.1%)	24 (33.8%)		
Lymph node involvement			**7.853‡**	**0.020**
0	**13 (18.8%)**	**8 (11.6%)**		
1	**10 (14.5%)**	**14 (20.3%)**		
2	**5 (7.2%)**	**19 (27.5%)**		
RAS			0.005‡	0.941
None	28 (21.2%)	45 (34.1%)		
Yes	23 (17.4%)	36 (27.3%)		
Life span (months)	58.00 (18.00-220.00)	22.30 (0.63-142.70)	-	-

(*) Independent Samples T Test; (†) Mann-Whitney U test; (‡) Pearson'S Chi-square Test; p< 0.05

Table 2. Laboratory values of living and deceased patients

Variable	Living	Exitus	t / Z	p value
	Average±SS/ The median (min-max)/ N (%)	Average±SS/ The median (min-max)/ N (%)		
WBC	8130 (3340-21730)	8470 (4300-20150)	-0.757†	0.449
HB	12.30 (8.50-15.20)	12.10 (8.00-16.20)	-0.753†	0.452
RDW	16.60 (12-26)	16.40 (13-30)	-0.435†	0.664
PNL	5120 (1100-18570)	5450 (2.84-16390)	-1.304†	0.192
Lymphocyte	**2050 (500-8300)**	**1710 (170-7200)**	**-2.568†**	**0.010**
Platelet (^10³)	304 (126-766)	301 (132-877)	-0.058†	0.953
MPW	8.80 (5.50-12.70)	8.90 (7.10-13.10)	-0.544†	0.587
PCT	0.29 (0.12-228.00)	0.28 (0.11-0.60)	-0.890†	0.373
Neutrophil-lymphocyte ratio (NLR)	**2.35 (0.50-19.33)**	**2.93 (0.00-82.12)**	**-2.648**	**0.008**
Platelet-lymphocyte Ratio	147.79 (32.40-391.34)	168.28 (48.71-1647.06)	-1.458†	0.145
CEA	**3.08 (0.72-141.70)**	**5.99 (1.03-1000.00)**	**-3.684†**	**<0.001**
CA19_9	**11.99 (0.60-1000.00)**	**20.63 (0.60-1998.00)**	**-3.111†**	**0.002**

(*) Independent Samples t test; (†) Mann Whitney U test; (‡) Pearson Chi-square test; p< 0.05

At the end of the correlation analysis applied to all data of all participants, it was observed that there was a negative correlation between life expectancy and age (r=-0.219, p=0.012), tumor stage (r=-0.201, p=0.021), MPW level (r=-0.224, p=0.010), mortality level (r=-0.585, p <0.001), CEA (r=-0.340, p <0.001) and CA 19-9 level (r=-0.228, p=0.009). With these findings, it was thought that when the patient is of advanced age, the life expectancy of the patients may be shortened as the tumor stage, MPW level, CEA, and CA 19-9 levels increase. In addition, it was thought that age, tumor stage, MPW, CEA and CA 19-9 levels could be predictors of life expectancy. In addition, there was a positive correlation between mortality rate and age (r=0.201, p=0.021), tumor stage (r=0.214, p=0.014), tumor invasion (r=-0.243, p=0.041), lymph node involvement (r=0.337, p=0.005) and NLR (r=0.231, p=0.008), CEA (r=0.323, p <0.001) and CA 19-9 (r=0.273, p=0.002) levels and a negative correlation with lymphocyte count (r=-0.224, p=0.010).

On the other hand, a positive correlation was found between WBC and CEA (r=0.252, p=0.004), CA 19-9 (r=-0.202, p=0.021) and NLR (r=-0.494, p<0.001) levels. A negative correlation was found between RDW level and hemoglobin (r=-0.521, p<0.001), MPW (r=-0.186, p=0.032) and NLR (r=-0.175, p=0.044) levels. A positive correlation was found between tumor invasion and lymph node involvement (r=0.425, p<0.001), RAS positivity (r=0.247, p=0.038) and mortality rate (r=0.243, p=0.041). In addition, a positive correlation was found between lymph node involvement and mortality rate (r=0.337, p=0.005). A positive correlation was found between smoking and the presence of metastasis (r=0.250, p=0.004), PCT level (r=0.190, p=0.029), CEA (r=0.199, p=0.023) and CA 19-9 (r=0.298, p=0.001) levels.

In addition, when correlation analysis was applied to the data of deceased people, the following results were reached. A negative correlation was found between life expectancy and age (r=-0.235, p=0.035) and CEA level (r=-0.270, p=0.016). In addition, a negative correlation was found between age and lymphocyte count (r=-0.228, p=0.041) and the presence of metastasis (r=-0.238, p=0.033). A positive correlation was observed between tumor stage and CEA (r=0.267, p=0.017) and CA 19-9 (r=0.317, p=0.004) levels. A positive correlation was observed between WBC number and CEA (r=0.241, p=0.031) and CA 19-9 (r=0.281, p=0.012) levels. There was a positive correlation between the presence of metastasis and smoking (r=0.315, p=0.004) and NLR level (r=0.226, p=0.043). Finally, there was a positive correlation between RAS positivity and CEA level (r=0.267, p=0.017).

At the end of the ROC-Curve test, which was applied to determine which of the study parameters were sensitive and specific in determining the mortality levels, it was found that age (threshold value >65 years, p=0.015), lymphocyte count (threshold value <1885, p=0.008), CEA (threshold value >3.42, p <0.001), CA 19-9 (threshold value >15.80, p=0.002) and NLR (threshold value >2.45, p=0.007) levels and lymph node involvement (threshold value > 4 and above lymph node involvement, p=0.007) may be sensitive and specific determinants in predicting the mortality rate.

At the end of The Logistic Regression Test, it was found that lymph node involvement (B=-1.821, Wald=7.291, p=0.007) and CEA level (B=0.014, Wald=4.761, p=0.029) may be the best parameters in predicting mortality rates.

On the other hand, Odds Ratio Test was applied for the effects of the parameters obtained at the end of the ROC-Curve Test on the mortality risk.At the end of this test, if the age was older than 65 years (OR=2.64, 95% confidence interval 1.28-5.42, p=0.008), if the CA 19-9 level was found to be more than 15.80 (OR=2.37, 95% confidence interval 1.16-4.86, p=0.018), and the NLR value was found to be more than 2.45 (OR=2.93, 95% confidence interval 1.42-6.06, p=0.004), the risk of mortality in these individuals was more than doubled.

When the participants were divided into four groups according to the stage of the tumor, tumor invasion level (X2=54.780, p<0.001), lymph node involvement (X2=47.200, p<0.001), presence of metastasis (X2=54.045, p<0.001) and PDW (X2=9.878, p=0.020), CEA (X2=12.447, p=0.006) and Ca 19-9 (X2=14.826, p=0.002) levels were found to be different between the groups.

As a result of the paired group comparisons, it was observed that PDW (Z=-2.634, p=0.008), CEA (Z=-2.740, p=0.006) and CA 19-9 (Z=-2.813, p=0.005) levels were different in people with stage 2 and stage 4 tumors. In addition, CA 19-9 values were found to be different in patients with stage 3 and stage 4 tumors (Z=-2.894, p=0.004).

In addition, when the participants were divided into two groups as RAS positive and RAS negative, only CEA levels were found to be different between the groups in terms of study data (Z=-2.356, p=0.018) (**Figure 1, Table 3**).

Metastasis was found to be higher in patients with stage 4 tumors and CEA and CA 19-9 levels were found to be high in these patients (**Figure 2, 3**).

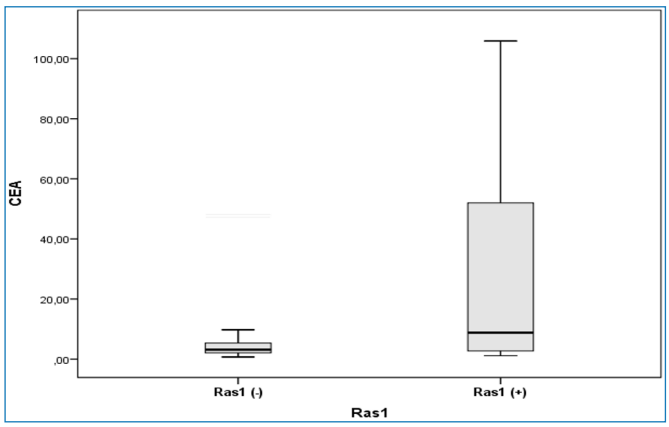

Figure 1. RAS mutation and CEA level comparison

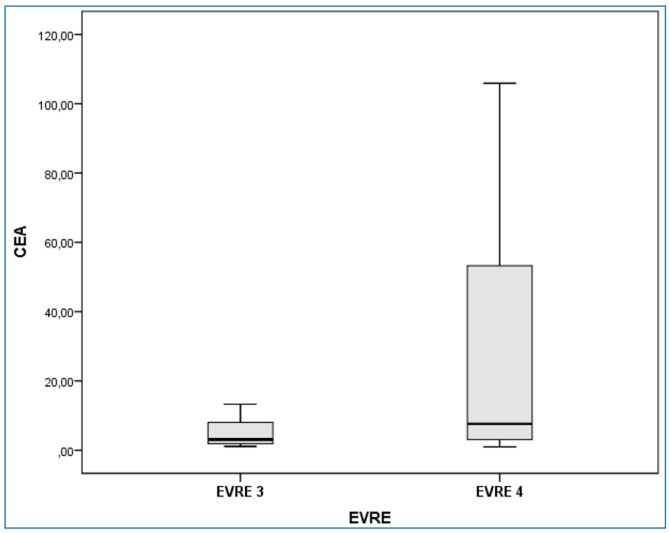

Figure 2. Comparison of Stage 3 and Stage 4 CEA level

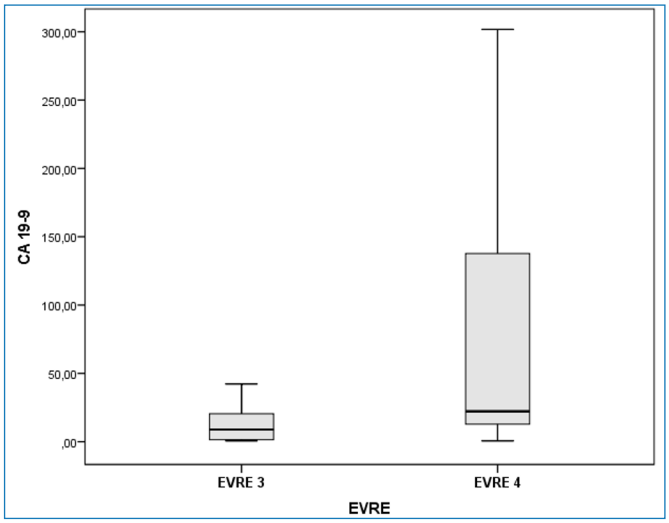

Figure 3. Comparison of Stage 3 and Stage 4 CA19-9 levels

Table 3. Evaluation of variables according to RAS status

Variable	RAS (-) Average±SS/ The median (min-max)/ N (%)	RAS (+) Average±SS/ The median (min-max)/ N (%)	t / Z	p value
Age	65.11±13.53	64.20±14.07	0.376*	0.708
Gender				
Male	46 (34.8%)	36 (27.3%)	0.055 ‡	0.814
Female	27 (20.5%)	23 (17.4%)		
Stage				
1	9 (6.8%)	3 (2.3%)	3.563‡	0.313
2	14 (10.6%)	9 (6.8%)		
3	17 (12.9%)	12 (9.1%)		
4	33 (25.0%)	35 (26.5%)		
Tumor				
1	1 (1.4%)	0 (0.0%)	4.435 ‡	0.218
2	4 (5.6%)	1 (1.4%)		
3	22 (31.0%)	9 (12.7)		
4	17 (23.9%)	17 (23.9%)		
Lymph node involvement				
0	15 (21.7%)	6 (8.7%)	1.578 ‡	0.454
1	16 (23.2%)	8 (11.6%)		
2	13 (18.8%)	11 (15.9%)		
Metastasis				
None	27 (30.3%)	13 (14.6%)	2.462 ‡	0.117
Yes	25 (28.1%)	24 (27.0%)		
Survey				
Living	28 (21.2%)	23 (17.4%)	0.005 ‡	0.941
Exitus	45 (34.1%)	36 (27.3%)		
WBC	8850 (3340-21730)	8130 (4300-20150)	-0.927†	0.354
HB	12.30 (8.50-16.20)	12.10 (8.00-15.80)	-0.222†	0.824
RDW	16.40 (12-30)	16.80 (13-28)	-1.485 †	0.137
PNL	5450 (1500-18570)	5160 (1100-16380)	-0.989†	0.323
Lymphocyte	1960 (500-8300)	1870 (170-3990)	-1.213 †	0.225
Platelet (^10³)	316 (126-877)	289 (132-666)	-1.014 †	0.311
MPW	8.75 (5.50-13.10)	9.20 (7.20-12.70)	-0.679 †	0.497
PDW	15.90 (14.00-18.20)	15.90 (11.40-17.60)	-0.220†	0.826
Neutrophil-lymphocyte ratio (NLR)	2.46 (0.88-19.33)	2.89 (0.00-82.12)	-0.428†	0.669
Platelet-lymphocyte Ratio	163.24 (32.40-712.87)	158.91 (54.10-1647.06)	-0.563 †	0.573
PCT	0Ç30 (0.11-228.00)	0.28 (0.11-0.60)	-1.087 †	0.277
CEA	3.33 (0.72-1000.00)	8.81 (1.13-1000.00)	-2.356 †	0.018
CA19_9	14.90 (0.60-1000.00)	18.27 (0.60-1998.00)	-0.684†	0.494

DISCUSSION

As it is known, CRC ranks third among the most common cancer types in the world. As with all types of cancer, inflammation causes cancer cells to spread and grow in CRCs. Inflammatory cells around the tumor have significant effects on tumor growth and spread, and it has been hypothesized that systemic inflammation markers may be useful to indicate prognosis.[13] In the studies conducted by Bambace and Holmes in 2011, and Goubran et al. in 2014, platelet cells are also involved in inflammation and have been shown to cause cancer cells to grow, angiogenesis and progress. In the studies conducted by Chadha et al. in 2015; Feng et al. in 2016, Heng and Benjapibal in 2014, Josa et al. in 2015, and Li et al. in 2014, found that platelets are an indicator of poor prognosis for many types of cancer.[14] In our study, the number of platelets did not change between stages and according to the presence of RAS mutation. This can be attributed to the disproportionate distribution of the number of patients between stages.

Lin et al.[15] found that PDW value was high in CRC patients in their study conducted in 2018.

To the best of our knowledge, no study has been conducted in the literature to determine whether there is a relationship between RAS-positive colon cancer and PDW. In our study, we aimed to show whether there is a relationship between RAS mutation and PDW in patients with colon cancer. In our study, 73 (55.3%) of the patients did not have a RAS mutation, 59 (44.7%) had a RAS mutation, and no parameters other than CEA level were found to be different between individuals, and only CEA levels of RAS positive individuals were found to be higher than RAS negative individuals. In addition, the level of PDW was found to be high in people with advanced stage tumors. In our study, it was found that the PDW value increased significantly as the stage progressed in CRC. This supports that PDW elevation can be used to indicate prognosis. It is predicted that the high PDW value may reflect the activated platelet level associated with tumor invasion and metastasis.

VEGF is associated with prognosis in many types of cancer, and circulating VEGF is mainly found in platelets and neutrophils.[16] Circulating active platelets release VEGF, which can trigger cancer invasion and metastasis. This condition can be associated with increased inflammation and, as a result, increased platelet count. The increase in inflammation and platelet count increases with stage and may cause an increase in PDW. The presence of inter-stage metastasis and increased PDW can also be attributed to VEGF release from activated platelets and secondary tumor invasion and metastatic effect. RAS mutation is a mutation in the EGFR pathway. In our study, the absence of PDW difference between RAS mutant and non-RAS mutant may suggest that thrombocytosis and PDW increase are independent of the EGFR pathway and effective on VEGF.

In addition, many studies have found a significant relationship between stage and MPV level increase in lung cancer, gastric cancer, hepatocellular cancer, endometrial cancer and colon cancers.[17]

White blood cell (WBC) count and neutrophil/lymphocyte ratio (NLR) have been investigated for their prognostic properties in some types of cancer. Walsh et al.[18] showed that NLR ≥5 was a marker of survival in colorectal cancer patients. In many studies, NLR increase has been associated with poor prognosis in cancer types.[19] In our study, it was found that if the age was older than 65, the CA 19-9 levels were found to be more than 15.80, and the NLR value was found to be more than 2.45 (OR=2.93, 95%, confidence interval 1.42-6.06, p=0.004), the risk of mortality in these individuals could be more than doubled. In addition, the increase in NLR in our study was positively correlated with the mortality rate, which was attributed to the low lymphocyte count in CRC patients with increased mortality. RAS mutations, which are an indicator of a poor prognostic factor in CRCs, were found to be higher in patients with NLR above 3. However, in our study, no significant difference was found between NLR value in RAS positive and RAS negative patients (p=0.669). This result may be due to the retrospective nature of our study and the limited number of our patient population.

CEA is a tumor marker commonly used to indicate prognosis in CRC patients.[20] In a study conducted by Li et al.[21] in 2013, it was revealed that the CEA level was high in patients with high NLR. In a study conducted in Thailand, a statistically significant difference was found in 5-year survival between low CEA level cancer and high CEA level cancer.[22] Similarly, our study shows that high NLR value and high CEA and CA 19-9 levels shorten life expectancy (p=0.008, p=<0.001, p=0.002). Instead of using tumor markers alone in long-term follow-up, the use of CEA and CA19-9 together has proven to have stronger results in showing the prognosis.[23] In our study, both CEA and CA19-9 were found to be high in patients who died and were shown to be associated with mortality. This shows us that CEA and CA19-9 tumor markers can be used not only in treatment follow-up but also to indicate the prognosis of the disease.

RAS mutations are more aggressive than other mutations and are associated with an increased risk of recurrence and death in patients with CRC.[24] In our study, a positive correlation was observed between RAS positivity and CEA level (r=0.267, p=0.017). Thus, it was thought that the life span of RAS positive individuals may have been shortened.

Tumor stage is the most important prognosis indicator in CRCs.[25] Moghimi-Dehkordi et al.[26] and Chapius et al.[27] stated that the universe should be considered as a major prognostic factor in their studies examining the prognostic factors of CRC. In a retrospective study conducted by Küçüköner et al.[28] with 767 patient data, 5-year disease-free survival rates decreased as the stage progressed. In our study, there was a negative correlation between life expectancy and age (r=-0.219, p=0.012), tumor stage (r=-0.201, p=0.021), MPW level (r=-0.224, p=0.010), mortality level (r=-0.585, p<0.001), CEA (r=-0.340, p < 0.001) and CA 19-9 level (r=-0.228, p=0.009). With these findings, it was thought that the patient's life expectancy could be shortened as the patient's advanced age, tumor stage, MPW level, CEA, and CA 19-9 levels increased. In addition, it was observed that the level of tumor invasion, involvement of more than 4 lymph nodes, and the presence of metastasis were higher in advanced stage tumor patients. In addition, PDW, CEA and CA19-9 levels were found to be higher in people with advanced stage tumors.

Smoking is a risk factor in CRCs as in many cancers. In the study of Kutlu et al. investigating the relationship between smoking and cancer, the incidence of CRC was found to be 1.11 times higher in smokers. There was a positive correlation between the presence of metastasis and smoking

(r=0.315, p=0.004) and NLR level (r=0.226, p=0.043). Thus, it was predicted that the likelihood of metastasis may increase in people who smoke, and in this case, the life span of the person may be shortened indirectly.

As it is known, the first thing to do before treatment in colon cancer is to determine the stage of the disease. Lymph node involvement is the most important parameter in determining the stage of the disease.[30] In a retrospective study conducted by Benedek et al.[31] in 2020 by prioritizing the lymph node status in Romania, it was revealed that the most important prognostic factor in 5-year survival was lymph node status. In the study conducted by Ortega et al.[32] in 2017, the 5- and 10-year disease-free survival of surgically removed lymph nodes in stage 2 CRC patients was found to be 86.5% in those with more than 12 lymph nodes resected. In many studies in the literature, it is recommended to remove at least 12 lymph nodes during surgery, especially in stage 2 patients. In our study, it was shown that lymph node involvement was sensitive with age, lymphocyte count, CEA, CA19-9 levels in predicting mortality rate. This situation supports that lymph node involvement is an indicator of prognosis with stage. In our study, it was revealed that the number of lymph nodes kept in predicting life expectancy may be an important parameter, and it was observed that the detection of lymph node involvement in our study increased the risk of mortality in CRC patients by more than 3 times. In addition, in our study, it was observed that the number of metastatic lymph nodes was higher in patients who died than in living patients (p=0.020). This situation supports that as the number of lymph node involvement increases, the stage and mortality rate increases and lymph node involvement is an important criterion in determining the prognosis.

CONCLUSION

Previously, many studies have investigated the relationship between cancer and platelet indices, but to the best of our knowledge, it has not been evaluated together with the RAS mutation. In our study, the relationship between RAS mutation and PDW was investigated, but no significant relationship was found between the two. A low level of correlation coefficient but a significant positive correlation was found between stage and PDW. This may be associated with an increase in inflammation level as the stage increases. A significant relationship was found between the presence of RAS mutation and only CEA level and mortality. This result may be due to the narrow patient population of our study and the insufficient number of patients. More studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 16.06.2021, Decision No: 111).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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